# Recombinant DNA Advisory Committee and Genetic Modification Clinical Research Information System

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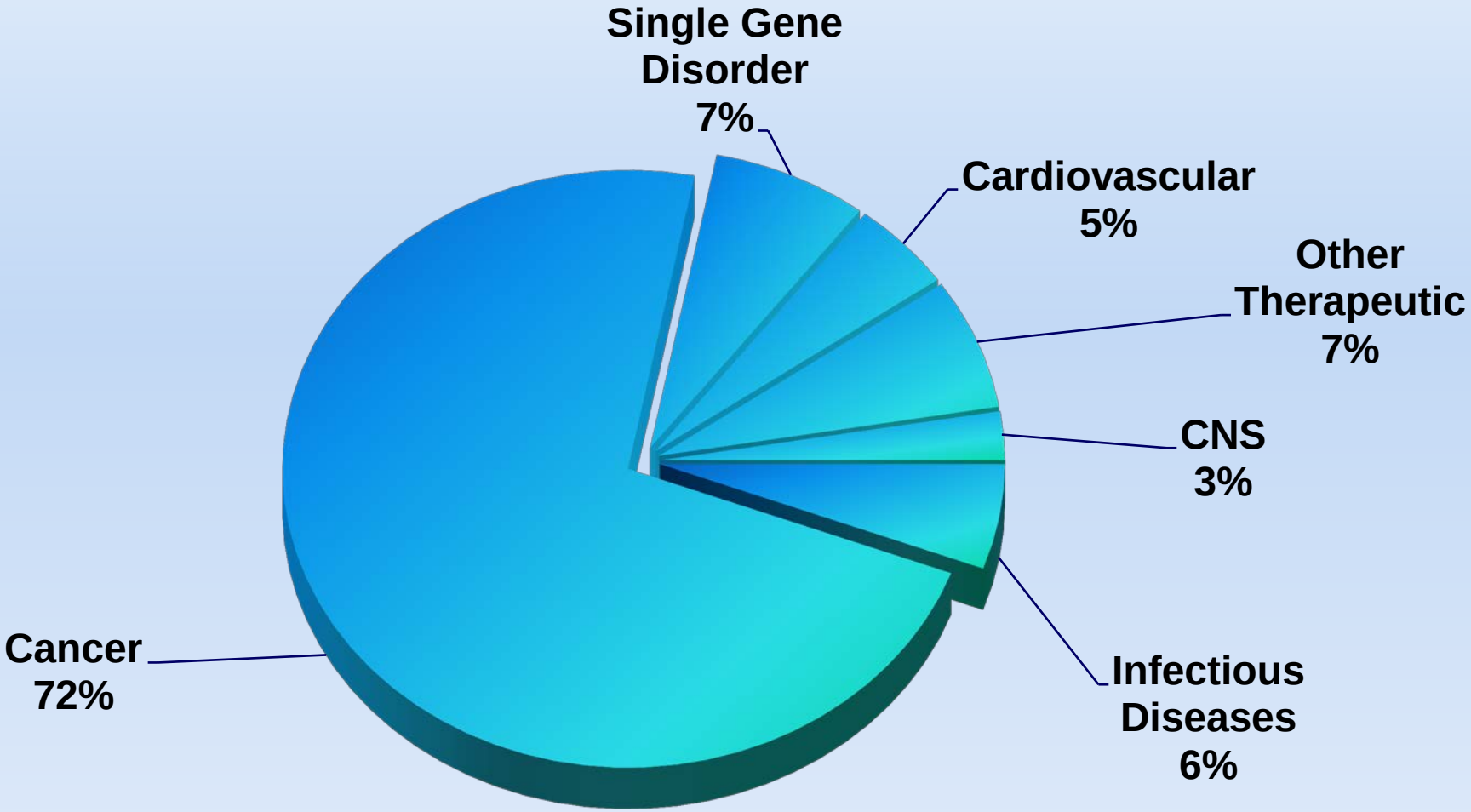
**Office of Biotechnology Activities**
**Office of Science Policy**
**April 12, 2013**

National Institutes of Health
Office of Biotechnology Activities

# OVERVIEW

- Clinical Gene Therapy:  Applications and Vectors
- Role of the RAC and Resources
- The Genetic Modification Clinical Research Information System (GeMCRIS)

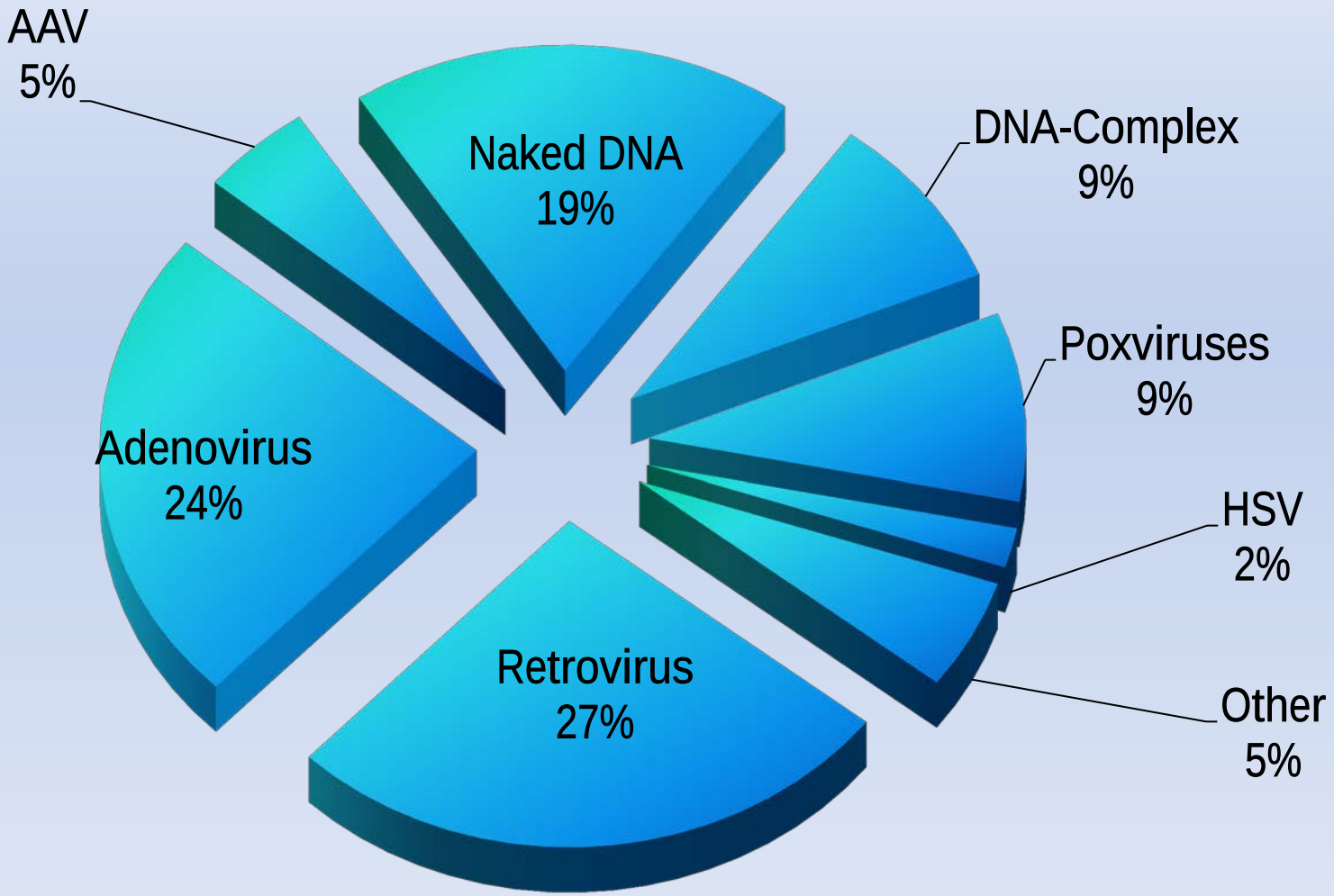
# Gene Transfer Trials By Application 2008-2012






*Rev: 08-16-12err*

# Gene Transfer Trials By Delivery System 2005-2012



# Recombinant DNA Advisory Committee (RAC)

- Federal scientific advisory committee with broad clinical and scientific expertise as well as bioethics and public representation
- Meets quarterly in open forum with significant webcast audience
  - Promotes scientific rigor and ethical conduct of human gene transfer
  - Key component of biosafety oversight framework for recombinant and synthetic nucleic acid research conducted in the U.S.

# Clinical Protocol Review Activities

- **A small number of novel clinical human gene transfer protocols reviewed at public meetings**
  - **Enhances the scientific merit of the protocol**
  - **Increases the safety for subjects, and as necessary, biosafety protections for researchers, health care workers, close contacts of research subjects**
  - **Informs the field of new developments**
  - **Promotes transparency**

# Resources from Individual Protocol Reviews

- Was a Protocol reviewed?
  - GeMCRIS
  - Protocol List on OBA website
- Meeting materials
  - Webcast
  - Presentations
  - Minutes contain final RAC recommendations
  - Summaries of selected, related, serious adverse events reviewed by the Gene Transfer Safety Assessment Review Board (GTSAB)

http://oba.od.nih.gov/rdna/rdna.html

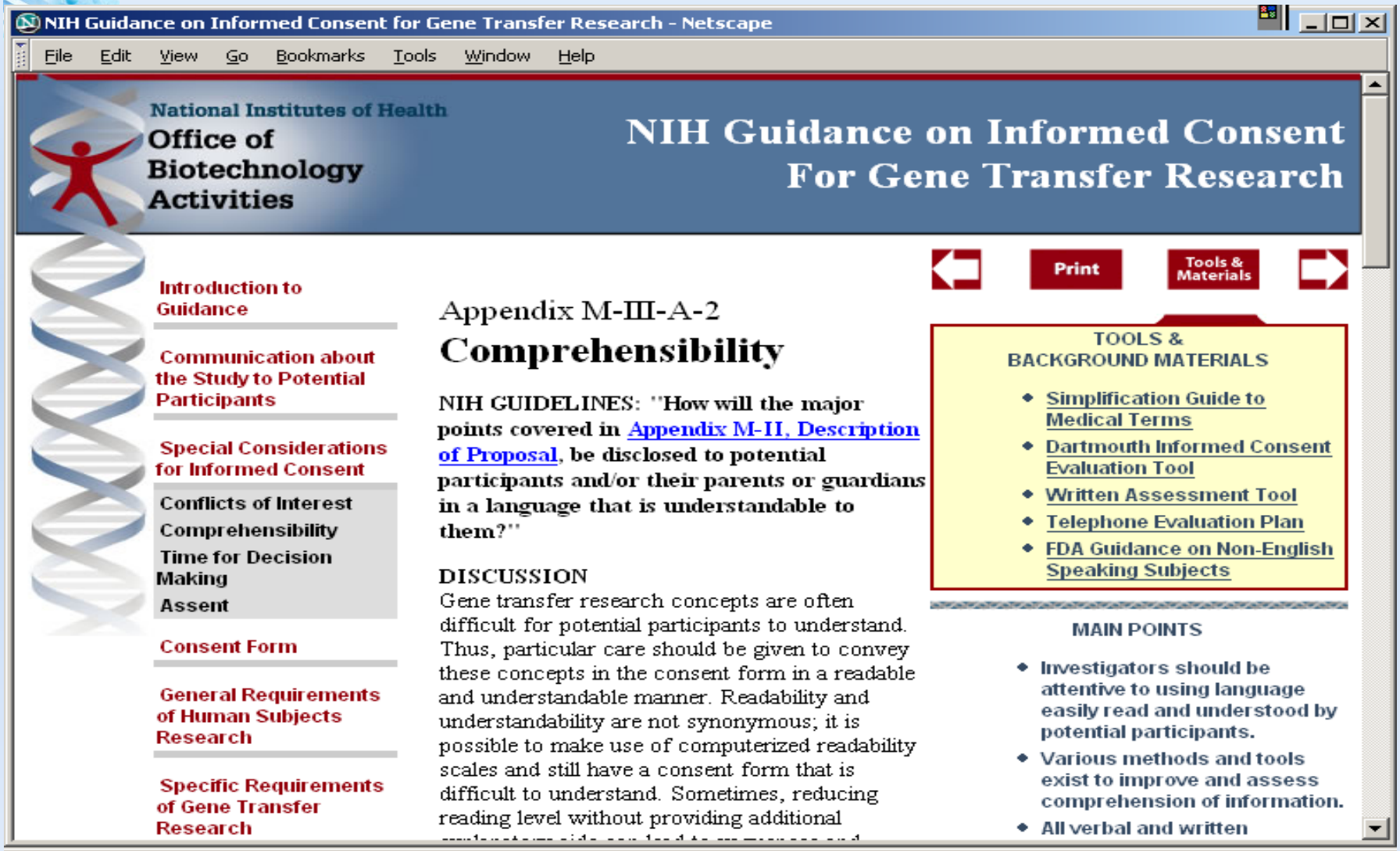
# Aggregation of Data from Protocols

- Ongoing identification and dissemination of key issues of importance to the field
  - Analyses of safety data:
    - Becomes the basis of safety symposia examining specific products/trial designs
    - Assures the public that potential safety issues are being proactively addressed
  - Identification of trends in protocol design, applications, and vectors to allow development of gene therapy workshops

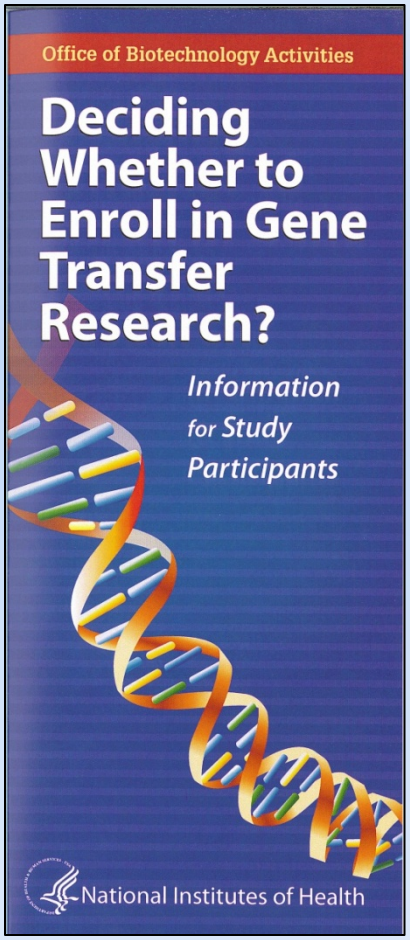
# Recent Workshops

- Gene Transfer and Rare Diseases (Sept. 2012)
- RNA Oligonucleotides: Emerging Clinical Applications (Dec. 2011)
- NIH RAC and CliniGene Scientific Symposium on Retroviral and Lentiviral Vectors for Long-term Gene Correction: Clinical Challenges in Vector and Trial Design (Dec. 2010)
- Sham Neurological Procedures in Clinical Trials for Neurodegenerative Diseases: Scientific and Ethical Considerations (June 2010)
- Gene-Modified T Cells: Challenges in Clinical Trial Design (June 2010)

# Informed Consent Guidance



# Other Resources




- **Helps potential participants understand fundamental concepts in human gene transfer research**
- **Suggests questions participants should pose to their physicians and to research staff in order to make a fully informed decision about participation**

# GeMCRIS

- **Launched in 2004, GeMCRIS® is a Web-accessible database of human gene transfer clinical trials accessible by all.**
- **GeMCRIS is also a relational database that supports Web-based reporting of adverse event information directly to NIH.**
- **The development of GeMCRIS was a collaborative effort involving both the NIH and the FDA. Adverse event (AE) information captured in GeMCRIS also meets FDA reporting requirements.**

# GeMCRIS

- **OBA and FDA can use GeMCRIS to analyze protocol and safety data**
  - **# of protocols using a vector**
  - **# of subjects dosed**
  - **Safety data can be searched across all 1200+ protocols based on event terms, MeDRA codes, relationship to gene transfer agent, vector, time interval between dosing and event**

# GeMCRIS Analysis

- In June 2011, OBA was notified of an unexpected death of a subject with leukemia on cancer vaccine trial
- Vaccine consisted of irradiated K562 cells transduced with a gene for human GM-CSF
- An unexpected finding in this case was the development of a profound eosinophilia with eosinophilia counts of > 100,000/ul and high circulating levels of GM-CSF

# GeMCRIS Analysis

- OBA notified 26 investigators with active protocols that either used K562 cells transduced with a gene for GM-CSF or irradiated tumor cells with GM-CSF
- OBA was able to notify the investigators that of the 71 protocols using these products, which together had dosed over 1700 subjects, only one other event with a mild, self-limiting eosinophilia was discovered
- Investigators invited to watch the webcast of the RAC meeting discussing this event and given the opportunity to participate

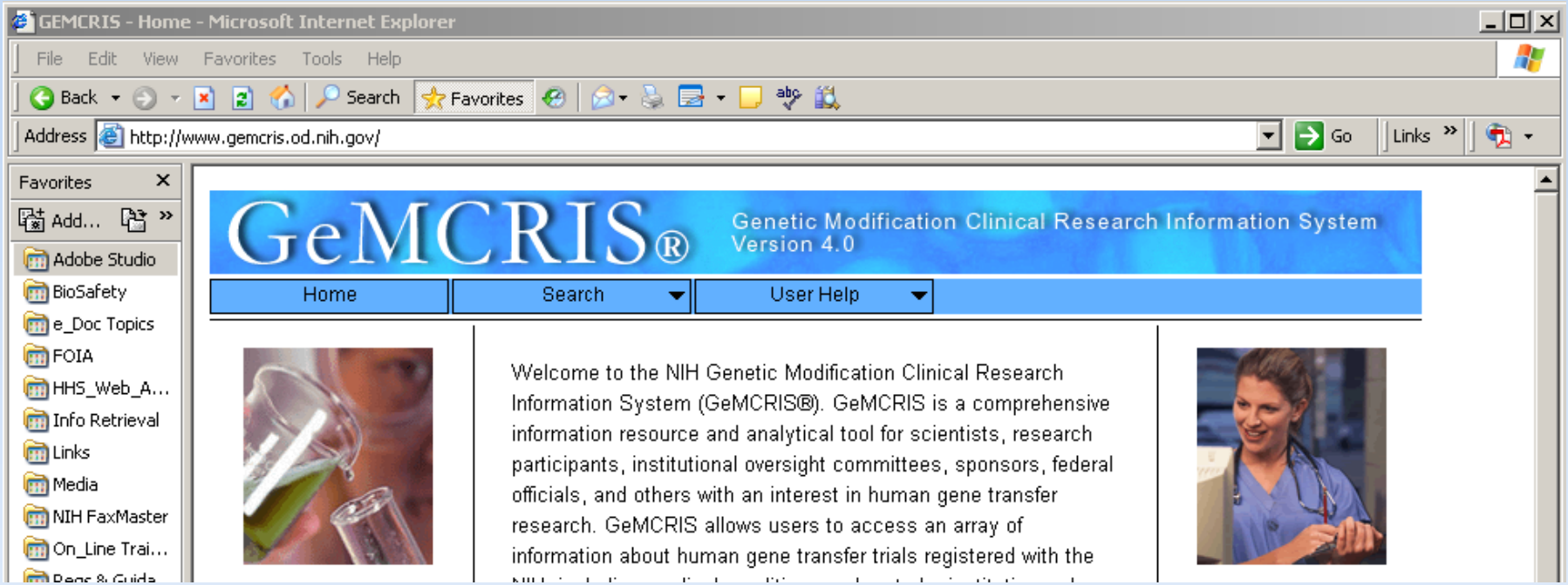
# Public Access to GeMCRIS

- Promotes public access to information and understanding about human gene transfer clinical research
- Provides additional information that is not included in other data bases, such as Clinical Trials.gov
  - Detailed information on product, including vector, promoters and specific transgenes
  - Scientific and non-scientific abstracts
  - Links to minutes if public review done
  - Summaries of major trial design changes

# Public Access to GeMCRIS

- Type the following URL into your Web browser's address bar:

  **http://www.gemcris.od.nih.gov/**



# Finding Information

**All clinical trial information is accessed through the "Search" functions on the Menu Bar**

Search functions include:

- Protocol title and OBA Protocol numbers
- Medical condition (MedDRA coded)
- Trial Sites, study phase and trial status
- Product searches by:
  - -Product name (includes synonyms e.g. "TK")
  - -Descriptors (controlled vocabulary)
  - -Vectors, genetic elements, producer cells
  - -Routes of administrations

# Finding Information

## Search Protocol Data

GeMCRIS® Genetic Modificati Version 6.2

Home | Search | User Help

- Protocols
- Principal Investigators
- Vocabulary Reports

Search by Condition/Title

Search by Product

(GeMCRIS®). GeMCRIS i
information resource and analytical tool for sci
participants, institutional oversight committees
officials, and others with an interest in human
research. GeMCRIS allows users to access a
information about human gene transfer trials re
NIH, including medical conditions under study
trials are being conducted, investigators carryi
gene products being used, route of gene produ
summaries of study protocols.

To facilitate access to this information, GeMC
of preformatted reports. You can also create y
tailored to your particular information needs. T
the "Search" menu item above, or click the "F
Questions" link on the left to learn more about

Support

- Feedback
- Frequently Asked Questions
- Contact Us
- Browser Requirements

GeMCRIS® Genetic Modification Clinical Research Information System Version 4.0

Home | Search | User Help

You may search the protocols by selecting any combination of the parameters below. If you wish to see all the protocols within GeMCRIS, leave the search fields empty and click the 'Search' button at the bottom of the page. Be aware that selecting multiple criteria will return only those protocols that match all of the constraints given.

If you would like to search for protocols by product description, then use this Protocol Search by Product link.

Back

Protocol Report Query Menu

Clinical Trial Title

Medical Condition

OBA Protocol Number

--Select-- Search

Clinical Trial Site

--Select--

Principal Investigator

--Select--

Study Phase

--Select--

Status

--Select--

Search Reset

Site Map


**“Quick” display**

Protocol Number: 1103-1095

Title: A Phase I/II Study of the Safety and Feasibility of Administering T Cells Expressing Anti-EGFRvIII Chimeric Antigen Receptor to Patients with Malignant Gliomas Expressing EGFRvIII

Phase: I (Phase Disclaimer)

Status: Active - 10/12/2012

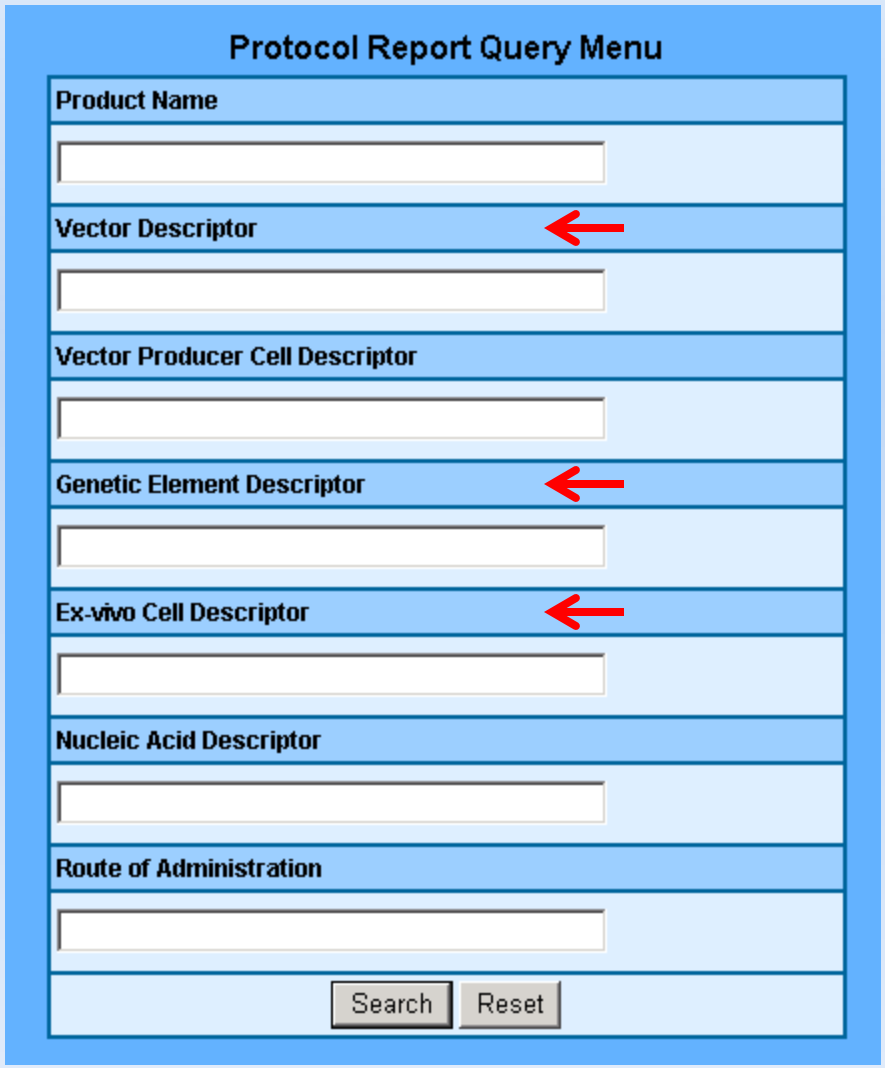
| | |
|---|---|
| Principal Investigator: | Rosenberg, Steven A, National Cancer Institute - NIH |
| Medical Condition: | Malignant glioma |
| Ex-vivo Cell:<br>Transducing Agent:<br>Genetic Element: | » Primary autologous T lymphocytes<br>» Envelope amphotropic Murine stem cell retrovirus gene transfer vector / PG13 packaging cell line<br>» Murine stem cell virus (PCC4 embryonal carcinoma cell-passaged myeloproliferative sarcoma virus) long terminal repeat<br>» Epidermal growth factor receptor scFv-CD28-CDzeta-41BB CAR<br>» 5' and 3' splice sites |
| Route of Administration: | |
| Recommendation: | Selected for Public Review |
| Public RAC Review Date: | 06/08/2011 |
| RAC Meeting Minutes: | http://oba.od.nih.gov/oba/RAC/meetings/June2011/RAC_Minutes_06-11.pdf |

| Date | RAC Review Date | Type | Summary |
|---|---|---|---|
| 09/30/2011 | 12/13/2011 | M-I-C-1 Response | This submission is the 20 day letter notifying OBA that the trial has been initiated. |

## HYPERLINKS:

- Investigator(s),
- Vector, cells, genes
- RAC minutes
- Abstracts
- Clinicaltrials .gov
- Amendments

# Finding Information
## Search Product Data




Product Name:

- Shorthand or other designations of constructs (e.g. GVAX, JX-594…)

Biological Descriptors:

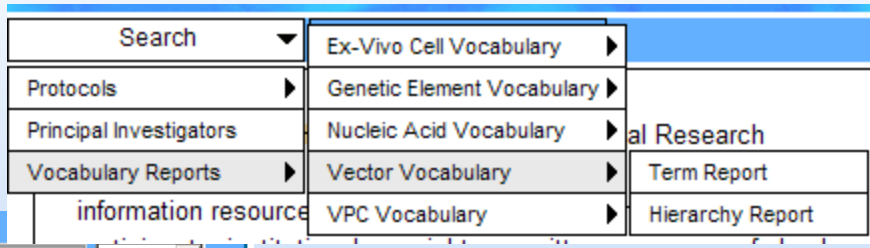
- Vector Classes
- Producer Cells
- Genetic elements
- Transduced Cells

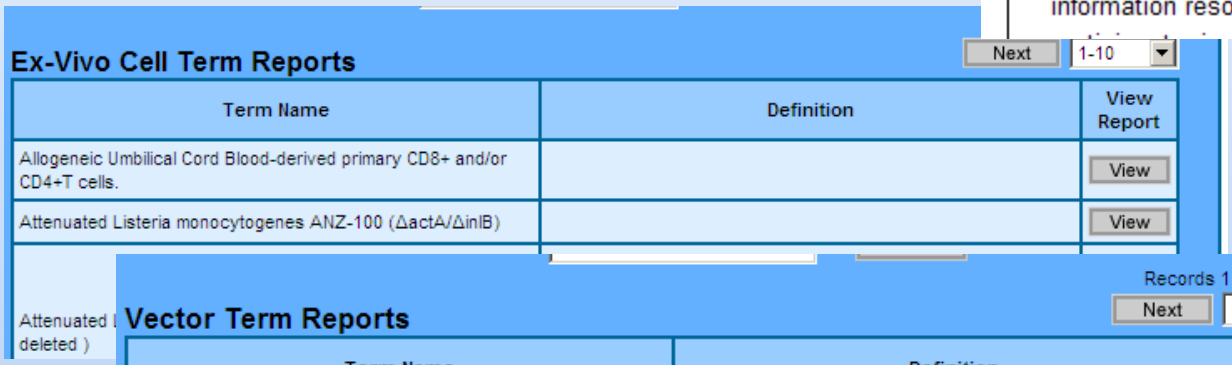
Routes of Administration

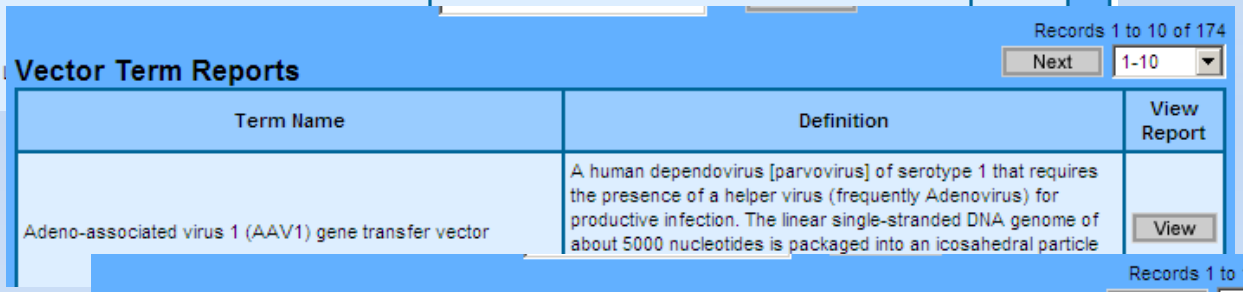
Multiple field entries return filtered data (“and” logic)

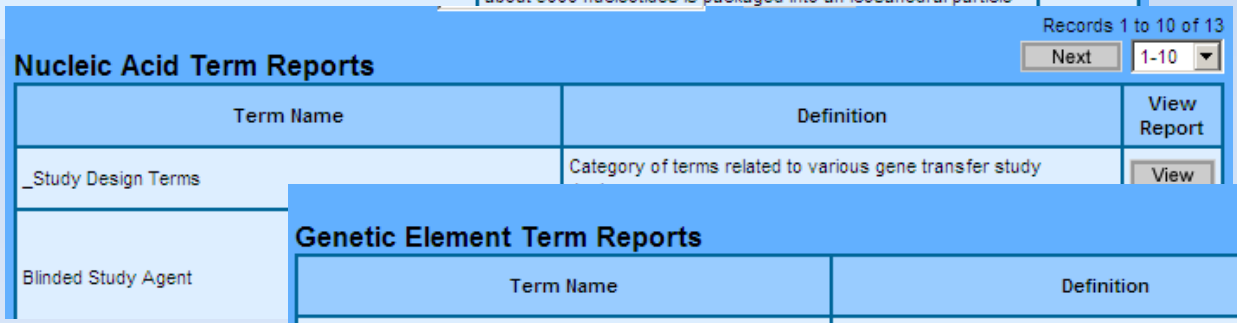
# Vocabulary Reports

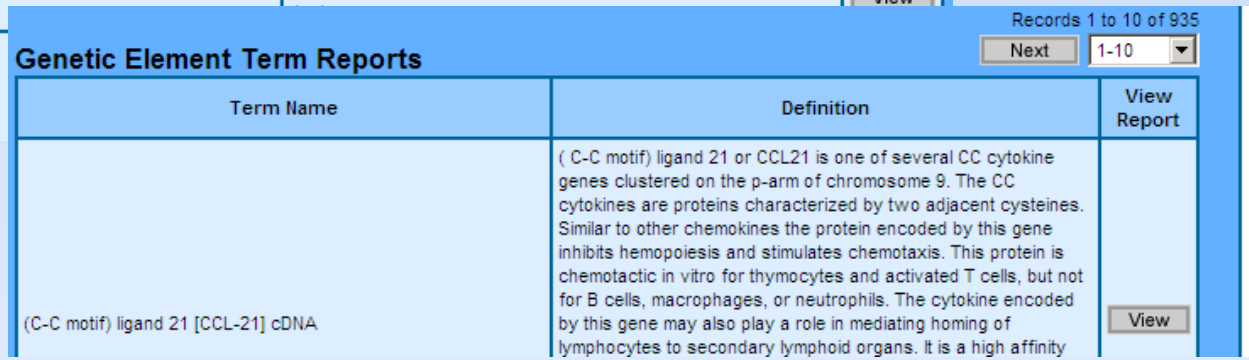
## Term Reports



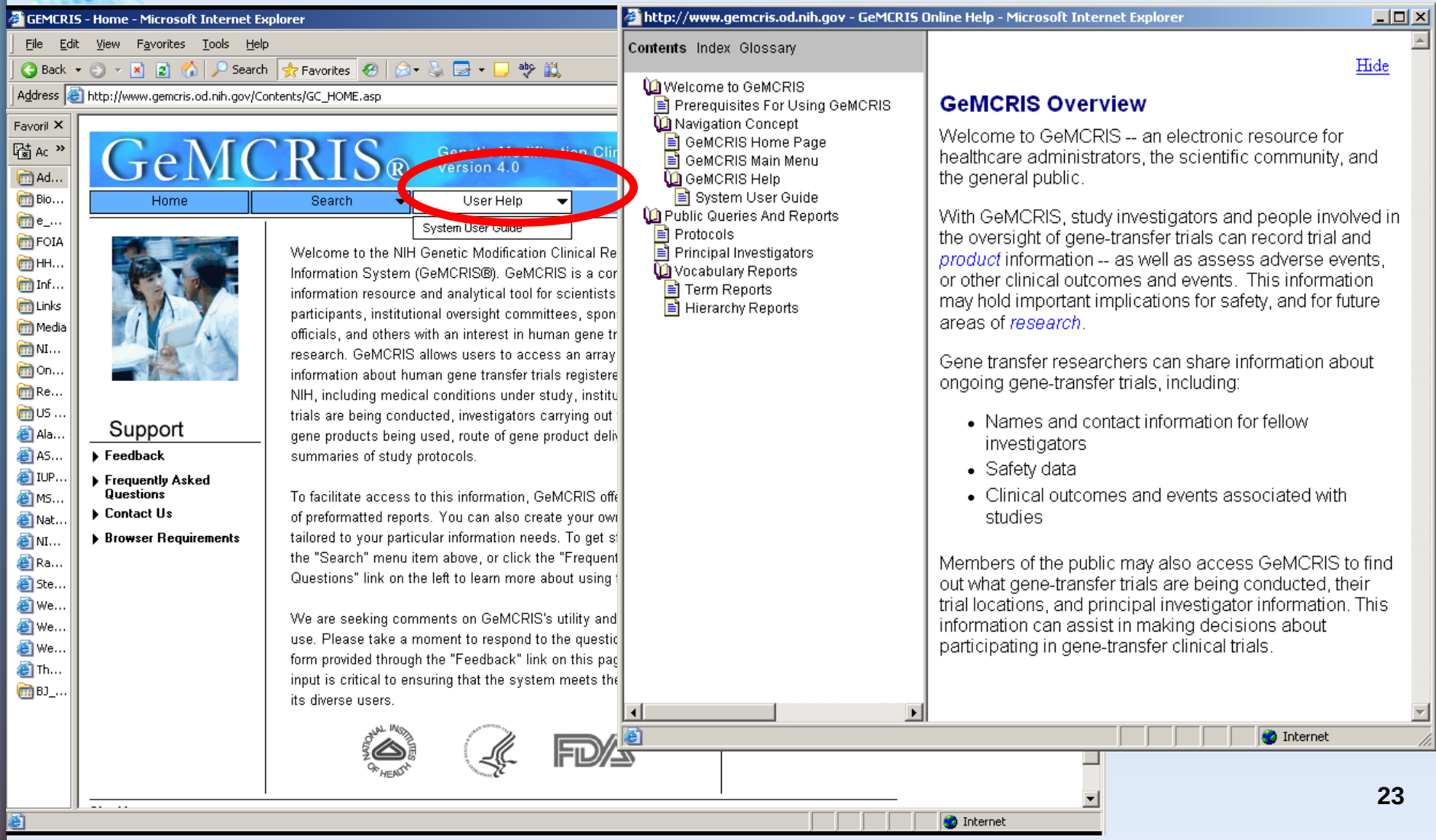



# User Help


GEMCRIS - Home - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.gemcris.od.nih.gov/Contents/GC_HOME.asp
GeMCRIS®
version 4.0
Home
Search
User Help
System User Guide
Welcome to the NIH Genetic Modification Clinical Re
Information System (GeMCRIS®). GeMCRIS is a cor
information resource and analytical tool for scientists
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trials are being conducted, investigators carrying out
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Questions" link on the left to learn more about using
We are seeking comments on GeMCRIS's utility and
use. Please take a moment to respond to the questic
form provided through the "Feedback" link on this pag
input is critical to ensuring that the system meets the
its diverse users.
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Feedback
Frequently Asked Questions
Contact Us
Browser Requirements
NATIONAL INSTITUTES OF HEALTH
FDA
Internet
http://www.gemcris.od.nih.gov - GeMCRIS Online Help - Microsoft Internet Explorer
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GeMCRIS Help
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Principal Investigators
Vocabulary Reports
Term Reports
Hierarchy Reports
Hide
GeMCRIS Overview
Welcome to GeMCRIS -- an electronic resource for healthcare administrators, the scientific community, and the general public.
With GeMCRIS, study investigators and people involved in the oversight of gene-transfer trials can record trial and product information -- as well as assess adverse events, or other clinical outcomes and events. This information may hold important implications for safety, and for future areas of research.
Gene transfer researchers can share information about ongoing gene-transfer trials, including:
Names and contact information for fellow investigators
Safety data
Clinical outcomes and events associated with studies
Members of the public may also access GeMCRIS to find out what gene-transfer trials are being conducted, their trial locations, and principal investigator information. This information can assist in making decisions about participating in gene-transfer clinical trials.
Internet

# Enhancements to GeMCRIS

- **Selected amendment summaries are now posted to the public-facing GeMCRIS pages**

- **In addition to adverse event reports, investigators can submit Annual Reports directly to GeMCRIS**

**Office of Biotechnology Activities**
**6705 Rockledge Drive, Suite 750**
**Bethesda MD 20892**
**OBA@od.nih.gov**

**For information on upcoming meetings join our listserv.**

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# Gene Transfer Protocol Report

**Protocol Number:** 0401-624

**Title:** Phase I Trial of Conditionally Replication-Competent Adenovirus (Delta-24-RGD) for Recurrent Malignant Gliomas

**Phase:** I (Phase Disclaimer)

**Status:** Active - 6/9/2011

| | |
|---|---|
| **Principal Investigator:** | Conrad, Charles A., The University of Texas MD Anderson Cancer Center<br>Lang, Frederick F., The University of Texas MD Anderson Cancer Center |
| **Medical Condition:** | Brain neoplasm<br>Glioblastoma multiforme<br>Glioma |
| **Product References:** | Suzuki et al., 2001. A conditionally replicative adenovirus with enhanced infectivity shows improved oncolytic potency. Clin. Cancer Res. 7:120-126.<br><br>Dmitriev et al. 1998. An adenovirus with genetically modified fibers demonstrates expanded tropism via utilization of a coxsackievirus and adenovirus receptor-independent cell entry mechanism. J. Virol. 72 (12):9706-9713. |
| **Abstracts:** | Scientific Abstract Link<br>Non-Technical Abstract Link |
| **Link to ClinicalTrials.gov:** | http://www.clinicaltrials.gov/ct2/show/NCT00805376 |

**Amendments:**

| Date | RAC Review Date | Type | Summary |
|---|---|---|---|
| 07/05/2012 | 09/11/2012 | Annual Report | Annual report submitted. The study is open to enrollment. |
| 04/19/2012 | 06/19/2012 | Other | Amendment updates the language for reporting of adverse events to reflect the current policies and procedures for MD Anderson Cancer Center. |
| 02/08/2012 | 06/19/2012 | Other | Amendment updates the informed consent to include the latest information on side effects of dexamethasone. |
| 09/02/2011 | 12/13/2011 | Other | Amendment updates the informed consent document regarding providing access to patient information for purposes of study audits. For those subjects who are unable to consent (deceased, off-study or lost to follow-up) a waiver of consent is sought. |
| 06/09/2011 | 09/13/2011 | Annual Report | Annual report submitted. The study is open to enrollment. |